UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,086	12/23/2005	Peter J. Quesenberry	59441(11259)	3235

21874 7590 10/20/2009

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

MAIL DATE	DELIVERY MODE
10/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,086	QUESENBERRY, PETER J.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 54-64* is/are pending in the application.

4a) Of the above claim(s) *14-28 and 32-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,29-31 and 54-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant should note that the examiner for the case has changed.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/09 has been entered.

Response to Amendments

Applicant's amendments filed 8/11/09 to claims 1, 2, 30, and 31 have been entered. Claims 42-53 have been canceled. Claims 54-64 have been added. Claims 1-41 and 54-64 remain pending in the current application, of which claims 1-13, 29-31, and 54-64 are being considered on their merits. Claims 14-28 and 32-41 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Priority

Applicant requests acknowledgement of the claim for priority to two provisional applications, including 60/485,607. See reply, page 13, section III. The specification in the '607 provisional application appears to be identical to the instant specification. The

examiner notes that even if applicant were entitled to a filing date of 7/6/03, all of the cited references would still qualify as prior art.

Election/Restrictions

Applicant's request for reconsideration of the restriction requirement is improper and untimely. Examiner Afremova finalized the restriction requirement in an Office action mailed 3/24/08. If applicant believes there were errors in the restriction requirement, he is free to petition the Director. See 37 C.F.R. 1.144.

Claim Objections

Claim 1 is objected to because of the following informalities: The word "hematopoietic" is misspelled at the last line of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendments to the claims introduce numerous limitations that are not supported by the as-filed specification, which is extremely narrow in scope. The relevant

working example is limited to a few experiments in which unsorted bone marrow stem cells (BMSCs) are cultured in medium containing FLT-3 ligand, thrombopoietin, and steel factor; one in which Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells are sorted from BMSCs by FACS; and one in which some unspecified cells are cultured in a solid agar assay system with one of seven growth factors, then assayed for the formation of HPP-CFC and CFU-c. See page 11, lines 6-31, and page 12, line 15, through page 13, line 11. The working example does not appear to be an embodiment of the claimed invention, since there is no mention of cell cycle within the working examples. The specification generally discusses varying the phase of the cell cycle at which growth factors are added, but there is no support for the "determining" element of step (c) of claim 1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 29-31, and 54-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and its dependents

The language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., *In re Hammack*, 427 F 2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970); *In re Venezia* 530 F 2d. 956, 958, 189 USPQ 149, 151 (CCPA 1976); *In re Goffe*, 526 F 2d. 1393, 1397, 188 USPQ 131, 135 (CCPA 1975); *In re Watson*, 517 F 2d. 465, 477, 186 USPQ 11, 20 (CCPA 1975); and *In re Knowlton,* 481 F 2d. 1357, 1366, 178 USPQ 486, 492 (CCPA

1973). The courts have also indicated that before claimed subject matter can properly be compared to the prior art, it is essential to know what the claims do in fact cover. See, e.g., *In re Steele*, 305 F 2d. 859, 134 USPQ 292 (CCPA 1962); *In re Moore*, 439 F 2d. 1232, 169 USPQ 236 (CCPA 1969); and *In re Merat*, 519 F 2d. 1390, 186 USPQ 471 (CCPA 1975). In this case, claim 1 is so indefinite as to preclude a substantive search by the examiner. It is wholly unclear which steps are being performed, much less which steps would be included by the language and which would be excluded. The key deficiencies of claim 1 will be reviewed in turn.

Claim 1 is drawn to a method for the production of "cell cycle specific differentiated hematopoietic cells," a term that is confusing because it is not clear whether the product cells are at a specific stage of the cell cycle or whether they are differentiated to a particular step depending on which stage of the cell cycle is selected. Clarification is required.

Claim 1 includes 5 steps: a culturing step, a selection step, a determining step, a contacting step, and a subculturing step. However, only three of these appear to be active steps (culturing, contacting, and subculturing). Steps (b) and (c) appear to be an attempt to describe the end point of the method, the components of the culture medium, and the timing of the culture, but they do not do so effectively. It is not clear what criteria are employed for the "selecting" in step (b) or the "determining" in step (c). Clarification is required. The claim should clearly and distinctly identify the active steps and the materials necessary to carry out each step.

Step (a) requires culturing purified bone marrow stem cells (BMSCs) "for **cycle initiation** from resting state under conditions that promote **synchronous progression** through the cell cycle," which is confusing. It is not clear whether this step should yield cycle initiation or synchronous progression. The conditions do not appear to result in the stated purpose of the step. Clarification is required.

Step (b) recites the limitation "the synchronous purified [BMSCs]," which finds no antecedent basis in step (a). Steps (c) and (d) suffer similar deficiencies. Clarification is required.

It is not clear whether the phrase "for the at least one desired cell cycle specific hematopoietic cell type [ALODCCSHCT]" at the last line of step (b) refers to the selection, the contact, the growth factor, the cell cycle phase, the pathway, or some other portion of the sentence. Similarly, it is not clear whether the phrase "at a phase of the cell cycle favoring a specific differentiation pathway [POTCCFASDP]" refers to the selection, the differentiation, the contacting, or some other portion of the sentence. Clarification is required.

Step (c) requires determining the POTCCFASDP for the ALODCCSHCT, which appears to be a diagnosing-type limitation. In *Metabolite Laboratories Inc. v. Laboratory Corp. of America Holdings*, 71 USPQ2d 1081 (Fed. Cir. 2004), the CAFC concluded that claims to methods of assaying or diagnosing require a "correlating" step in which a particular test result is correlated unambiguously with a particular conclusion. See *Metabolite Labs* at 1088, *e.g.* In this case, there is no correlating step in the claims. Clarification is required.

Step (e) requires "subculturing the cells," but it is not clear to which cells in steps (a)-(d) this limitation refers. Furthermore, the language "wherein a plurality of the … cells **have** the at least one desired ... cell type" is queried. Clarification is required.

Claim 1 is replete with functional language, e.g. "under conditions that promote synchronous progression through the cell cycle"; "a phase of the cell cycle favoring a specific differentiation pathway for the at least one desired cell cycle specific hematopoietic cell type"; and "the at least one growth factor or cytokine to promote the specific differentiation pathway". While describing a product in terms of its function is not itself improper (see *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)), claims directed to a product should be distinguished from the prior art product in terms of structure rather than function; this point was recently revisited. "When a claim limitation is defined in purely functional terms, the task of determining whether that limitation is sufficiently definite is a difficult one that is highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the relevant art area). We note that the patent drafter is in the best position to resolve the ambiguity in the patent claims, and it is highly desirable that patent examiners demand that applicants do so in appropriate circumstances so that the patent can be amended during prosecution rather than attempting to resolve the ambiguity in litigation." *Halliburton Energy Services, Inc. v. M-I LLC*, 85 USPQ2d 1654, 1663 (Fed. Cir. 2008). Such ambiguity could be resolved in a few ways, for example by providing a quantitative metric for the property, or a formula for calculating the claimed functional property along with examples and counterexamples of products with that property.

While functional claiming is authorized by 35 U.S.C. § 112, sixth paragraph, that statute was enacted specifically to preclude overly broad claims that effectively purport to cover any and all limitations, so long as they perform the required functions. Specifically, claims that are ambiguous as to boundaries for functional limitations may be indefinite and do not distinguish the claimed product over the prior art. In this case, claim 1 gives absolutely no indication as to what properties constitute the "conditions" of step (a); the properties of a cell cycle phase that is "favorable" for a particular differentiation pathway in step (b); or the physical properties of the cytokine or growth factor with the "promoting" and "producing" effects of step (c). The examiner simply cannot determine the metes and bounds of the claims given the extremely verbose and vague nature of claim 1. Prolix claims are not allowable; see M.P.E.P. § 2173.05(m).

Overall, the language of claim 1 is so confusing as to be unreadable, precluding any meaningful further examination on its merits. The examiner calls applicants' attention to step (c) in particular, although each of the five steps employs vague and unintelligible language. The last four lines of step (c) do not comply with the rules of standard English; the phrase "upon with" has no clear meaning.

Because claims 2-13 and 29-31 depend from indefinite claim 1 and do not clarify these numerous points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 4 requires that the subculturing of claim 1 be "carried about for about 14 days," which is not standard English. Clarification is required.

It is not clear whether claim 5 further limits the method of claim 1 or whether it merely recites inherent properties of mid-S phase. Claim 11 suffers similar deficiencies regarding late S phase. Clarification is required.

Claim 12 includes matter in parentheses; it is not clear whether this limitation is optional or necessary for the claim. Clarification is required.

The term "differentiation hotspot" in claim 29 is not adequately defined in the specification, nor is it a term of art. At page 5, lines 23-28, the specification indicates that "differentiation hotspots" are "points where a specific differentiation pathway is favored," but it is not clear from this definition whether the hotspot is a set point in the cell cycle or whether it varies for each pathway and in what manner. Clarification is required.

Claim 30 requires that the predetermined phase comprise a "reversible differentiation hotspot," which is confusing because it is not clear whether the hotspot is reversible (i.e., sometimes it is a hotspot, sometimes it is not) or whether the differentiation itself is reversible. Furthermore, it is not clear how the limitations "a differentiated cell" and "a stem cell" relate to the cells recited in claim 1. Clarification is required. It is not clear whether claim 30 is an attempt to define a term or whether it is intended to further narrow claim 1.

Response to Arguments

Regarding the indefiniteness rejection of claim 30, applicant alleges that the "cellular de-differentiation is a concept known and understood for many years by those of ordinary skill in the art." Reply, page 14, section VII. These arguments have been

fully considered, but they are not persuasive. Claim 30 makes no mention of "cellular de-differentiation." Applicant's comments are not germane to the pending claims.

Applicant's comments do not overcome the new grounds of rejection above.

Claim 54 and its dependents

Claim 54, while not as verbose as claim 1, nevertheless suffers some of the same deficiencies. Specifically, claim 54 contains functional limitations that are not limited within the claim: "conditions that promote synchronous progression through the cell cycle" and "subculturing … until cell cycle specific differentiated hematopoietic cells are produced." The discussion of claim 1's functional limitations in view of *Halliburton* also applies to claim 54 for the same reasons. Claim 54 places no clear and definite limits on the nature of these culturing steps.

Claim 54 is drawn to a method for the production of "cell cycle specific differentiated hematopoietic cells," a term that is confusing because it is not clear whether the product cells are at a specific stage of the cell cycle or whether they are differentiated to a particular step depending on which stage of the cell cycle is selected. Clarification is required.

Step (a) requires culturing purified bone marrow stem cells (BMSCs) "for **cycle initiation** from resting state under conditions that promote **synchronous progression** through the cell cycle," which is confusing. It is not clear whether this step should yield cycle initiation or synchronous progression. The conditions do not appear to result in the stated purpose of the step. Clarification is required.

Claim 54 includes matter in parentheses; see the second-to-last line of the claim. It is not clear whether this limitation is optional or necessary for the claim. Clarification is required.

Because claims 55-64 depend from indefinite claim 54 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 57 suffers deficiencies identical to those described for claim 4. Clarification is required.

Claims 58 and 59 are confusing for the same reason that claims 5 and 11 are confusing. Clarification is required.

Claims 61 and 62 impose identical limitations as claims 29 and 30 and are therefore indefinite for the same reasons.

Claim 63 includes functional language "wherein the step of contacting … favors a specific differentiation pathway." This language is unclear for the reasons discussed at length above regarding claims 1 and 54. Clarification is required.

Claim 64 refers to "Lineage negative" cells, but the components of the relevant lineage panel are not included in the claim. Clarification is required.

Response to Arguments

Applicant's comments do not overcome the new grounds of rejection above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 13, and 29-31 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hagihara et al. (2001, *Journal of Immunological Methods* 253: 45-55; on 2/27/06 IDS).

As discussed at length in the indefiniteness rejections, above, claim 1 and its dependents are sufficiently vague as to be virtually unsearchable. However, in the interest of compact prosecution, the examiner has attempted to interpret these claims. The interpretation is for art rejection purposes only.

Claim 1 is interpreted as being drawn to a method for producing differentiated hematopoietic cells comprising culturing purified BMSCs under conditions that promote synchronous progression through the cell cycle, thereby yielding cell cycle-synchronized BMSCs; choosing a desired endpoint of differentiation and identifying a growth factor or cytokine that promotes differentiation of BMSCs toward that endpoint; and contacting the synchronized BMSCs at a particular phase of the cell cycle with that growth factor or cytokine until the desired endpoint of differentiation is reached by at least a plurality of the BMSCs. In some dependent claims, the growth factor or cytokine is selected from a list. In some dependent claims, the differentiation endpoint is pointed out. In some dependent claims, the properties of the culturing step are particularly described.

Hagihara teaches a method for the production of differentiated hematopoietic cells including dendritic cells wherein the method comprises culturing purified CD34+ bone marrow stem cells in a medium comprising steel factor, thrombopoietin, and FLT-3 ligand; then contacting the cells with growth factor GM-CSF; then subculturing the cells

with GM-CSF for 14 days. See section 2.4 at page 49.

M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application. In this case, even if applicant had identified some previously unappreciated properties of Hagihara's method steps (which the examiner does not concede), the steps themselves would not become patentable. See *Titanium Metals Corp. v. Banner,* 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

Regarding claim 13, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step.

As discussed above, claims 29-31 do not clearly limit the independent claims, in part because they appear solely to describe inherent properties of the steps.

Response to Arguments

Regarding the anticipation rejection of record, applicant alleges that the fact that Hagihara did not recognize that steel factor, thrombopoietin, and FLT-3 ligand promote synchronous progression through the cell cycle disqualifies the reference as anticipatory. See page 16. The examiner disagrees. Whether Hagihara recognized the synchronizing effect of their culturing step is immaterial, since the step necessarily results in any effects that are inherent to that step. There is no need for any so-called "motivation" to carry out the step. Hagihara teaches steps that are fully encompassed by the instant claims and therefore anticipates the claims.

Applicant alleges that Hagihara lacks sufficient detail as to the timing of the culturing to anticipate the claims. See page 16. The examiner disagrees; for the ample reasons set forth above, the limitations of claim 1 fail to effectively describe the "timing" conditions, much less to limit them such that they overcome the art. The examiner also wishes to note respectfully that claim 1 does not require culturing only purified BMSCs in step (a), since the method itself **comprises** the five steps. Additional cells may be included in step (a). See M.P.E.P. § 2111.03.

Applicant alleges that Hagihara "discloses a vague, imprecise, and random period of time," but as discussed above, the claim limitations themselves are vague and imprecise. There are no clear criteria for selecting a phase of the cell cycle and no requirements that the contact with the growth factor or cytokine occur only at some "predetermined" cell cycle phase -- again, claim 1 is drawn to a method **comprising** five steps, so additional culturing steps are reasonably included within its scope.

The examiner has fully considered the declaration submitted under 37 C.F.R. 1.132 by Peter Quesenberry (hereafter "the Quesenberry declaration"), but it is not persuasive of error. The Quesenberry declaration contains no data, so it constitutes opinion evidence. M.P.E.P. § 716.01(c) provides guidelines for assessing expert opinion evidence. In this case, the declaration seeks to establish that the prior art reference did not recognize certain features of the steps within its method, but as described above, such a consideration is immaterial to patentability. The declaration is wholly unsupported by factual evidence, and the declarant is the inventor, so it is reasonable to presume that he has an interest in the outcome of the case. The declaration appears to

state only conclusions, so it cannot overcome the anticipation rejection, especially given the vague and indefinite nature of the claims. Furthermore, the Quesenberry declaration shares no nexus with the instant claims. See M.P.E.P. § 716.01(b). The Quesenberry declaration refers to a “link” between particular phases of the cell cycle and particular cell types. See page 8. However, there is no such "link" recited or fairly implied by the claims. Since applicant's comments appear to be a substantial reiteration of the statements in the Quesenberry declaration, the examiner’s points above also apply to the declaration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 10, 11, 13, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara et al. (2001, *Journal of Immunological Methods* 253: 45-55) taken with Feng Yan et al. (2000, *Blood* 96: 680a) and Messner et al. (1987, *Blood* 70: 1425-1432).

As discussed at length in the indefiniteness rejections, above, claim 1 and its dependents are sufficiently vague as to be virtually unsearchable. However, in the interest of compact prosecution, the examiner has attempted to interpret these claims. The interpretation is for art rejection purposes only.

Claim 1 is interpreted as being drawn to a method for producing differentiated

hematopoietic cells comprising culturing purified BMSCs under conditions that promote synchronous progression through the cell cycle, thereby yielding cell cycle-synchronized BMSCs; choosing a desired endpoint of differentiation and identifying a growth factor or cytokine that promotes differentiation of BMSCs toward that endpoint; and contacting the synchronized BMSCs at a particular phase of the cell cycle with that growth factor or cytokine until the desired endpoint of differentiation is reached by at least a plurality of the BMSCs. Claim 54 is similar in scope to claim 1, except that the end point and cell cycle phase are limited. In some dependent claims, the growth factor or cytokine is selected from a list. In some dependent claims, the differentiation endpoint is pointed out. In some dependent claims, the properties of the culturing step are particularly described. In some dependent claims, the cell cycle phase is pointed out. In some dependent claims, some properties of the BMSCs are pointed out.

Hagihara teaches a method for the production of differentiated hematopoietic cells including dendritic cells wherein the method comprises culturing purified CD34+ bone marrow stem cells in a medium comprising steel factor, thrombopoietin, and FLT-3 ligand; then contacting the cells with growth factor GM-CSF; then subculturing the cells with GM-CSF for 14 days. See section 2.4 at page 49.

Regarding claim 13, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step.

As discussed above, claims 29-31 do not clearly limit the independent claims, in part because they appear solely to describe inherent properties of the steps.

Hagihara does not explicitly teach that the culturing of cells in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of the cells through the cell cycle. Hagihara does not indicate that the growth factor must be added during any particular cell cycle phase (although, as discussed above, the claims also make no such requirement; see M.P.E.P. § 2111.03).

Yan teaches that the combination of factors SCF, TPO and FLT-3 in the culture medium stimulates the hematopoietic bone marrow cells to enter into synchronous cell cycle from resting state. For example, see the abstract of Yan, which clearly discloses that the purified bone marrow cells were quiescent (non-diving or "resting" at G0/G1 phase) at the beginning of the culture, that the addition of cytokines SCF, TPO and FLT-3 stimulated the cells to enter into the cycle, and that the amount of synchronous cells in S phase increased during culturing in the presence of cytokines SCF, TPO and FLT-3.

Messner teaches that cell cycle studies and stem cell engraftment studies indicate that the higher than normal proportions of multipotential hematopoietic cells are present in S phase during progression of the hematopoietic cells through the cell cycles. See abstract, e.g.

A person of ordinary skill in the art would have had a reasonable expectation of success in synchronizing the BMSCs of Hagihara using Hagihara's medium containing SCF, TPO, and FLT-3 ligand because Yan teaches that such a medium promotes synchronous progression through the cell cycle. The skilled artisan would have been motivated to synchronize the cells in order to obtain more consistent results from the

culturing step, especially given Messner's teaching that the cell cycle phase affects the proportion of multipotential cells in a population.

The skilled artisan would have had a further reasonable expectation of success in synchronizing the cells and adding growth factor or cytokine (in this case, the GM-CSF of Hagihara) at various phases of the cell cycle because Messner teaches that more hematopoietic stem cells are at S phase than other cell cycle phases. The skilled artisan would have been motivated to determine the differentiability of Hagihara's stem cells at various points in the cell cycle in order to maximize the number of stem cells available for Hagihara's differentiation protocol. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (U.S. 2007). In this case, there are only a few different points in the cell cycle, and Messner teaches that these points were well known at the time of the invention; testing stem cells at each of these points to identify their propensity for differentiation would have constituted routine experimentation at the time of the invention.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to synchronize the cells of Hagihara with the medium of Hagihara and Yan and then to treat the synchronized cells at various points within the

cell cycle in order to determine the optimal conditions for Hagihara's differentiation method.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 7-9, 12, and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara, Yan, and Messner as applied to claims 1-6, 10, 11, 13, and 29-31 above, and further in view of Klabusay et al. (2002, *Blood* 100: Abstract No. 4118) and Ramsfjell et al. (1996, *Blood* 88: 4481-4492).

The claims are interpreted as above. Claim 54 is similar in scope to claim 1, except that the end point and cell cycle phase are limited. Claims 55-57 and 60-63 correspond to claims 2-4, 13, and 29-31, respectively.

The teachings of Hagihara are relied upon as above.

Regarding claim 60, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step.

As discussed above, claims 61-63 do not clearly limit the independent claims, in part because they appear solely to describe inherent properties of the steps.

Hagihara does not teach culturing in G-CSF. Hagihara does not teach all of the end points in claims 7-9, 12, and 54. Hagihara does not discuss the markers in claim 64.

Klabusay teaches that hematopoietic stem cells are able to regenerate

hematopoiesis in all lineages and that addition of G-CSF to their medium will significantly increase the number of maturated cells including granulocytes. See abstract, e.g.

Ramsfjell teaches that culturing stem cells in SCF enhances megakaryocyte differentiation, as well as production of granulocytes and other mature hematopoietic cell types. See abstract, e.g. Ramsfjell teaches that when megakaryocytes mature, they produce platelets. *Id.*

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the G-CSF of Klabusay or the SCF of Ramsfjell for the GM-CSF of Hagihara in Hagihara's method taken in view of Yan and Messner because Klabusay and Ramsfjell teach that G-CSF and SCF affect the differentiation of Hagihara's cells. The skilled artisan would have been motivated to make such a substitution to determine whether Hagihara's method can be used with Klabusay's and Ramsfjell's growth factors/cytokines to direct differentiation to the endpoints already associated by Klabusay and Ramsfjell with those growth factors/cytokines. Varying Hagihara's method using these two different growth factors/cytokines and assaying for directed differentiation to the limited outcomes taught by Klabusay and Ramsfjell would have constituted routine experimentation at the time of the invention. See *KSR* at 1397.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to vary the growth factor/cytokine in Hagihara's differentiation method in order to identify the effects of such variance on that method because Klabusay and Ramsfjell identified links between various growth factors and

particular differentiation endpoints.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara, Yan, Messner, Klabusay, and Ramsfjell as applied to claims 1-13, 29-31, and 54-63 above, and further in view of Herzog et al. (2003; *Blood* 102: 3483-3493; reference U).

The claim is interpreted as above, wherein the BMSCs comprise Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells.

The teachings of Hagihara, Yan, Messner, Klabusay, and Ramsfjell are relied upon as above. None of these references teaches starting with a population comprising Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells.

Herzog is cited solely as evidence that bone marrow inherently contains cells that are negative for a set of lineage markers and that exclude both rhodamine and Hoechst dyes ("$rhodamine^{lo}$ $Hoechst^{lo}$"). See page 3483, column 2. Claim 64 requires only that the BMSCs "comprise" Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells, so other cells may be present.

A person of ordinary skill in the art would have had a reasonable expectation that the cells of Hagihara contain Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells because Herzog teaches that these cells are an inherent component of BMSCs. A holding of obviousness is therefore clearly required,

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Regarding the obviousness rejections of record, applicant refers to the arguments provided against the anticipation rejection. See reply at page 20. These arguments are not persuasive for the reasons discussed above. The further comments (pages 21-22) have been considered, but they are also not persuasive of error. Generally, applicant's comments regard limitations not found in the claims, so they are wholly irrelevant to patentability. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant alleges (see page 21, first paragraph) that contrary to the teachings of Yan, the cells in the instant method are "cultured from dormancy to synchronous cycles," but the claims make no such requirement. Applicant's allegation that the instant method is a "two-step process" (see page 21, first paragraph), which is queried because claim 1 contains five enumerated steps and claim 54 contains three.

Applicant alleges that Klabusay and Ramsfjell did not recognize the importance of the selection of cell cycle phase. See page 21, paragraph 2. Applicant alleges that Messner did not correlate a choice of cell cycle phase with a particular differentiation endpoint. See page 21, paragraph 3. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800

F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Messner teaches a link between cell cycle phase and multipotency, while Klabusay and Ramsfjell teach a link between growth factor and endpoint. Combining all of the references relied upon indeed yields the claimed invention.

Applicant alleges that the person of ordinary skill in the art would not have considered the invention "obvious to try," but the examiner disagrees. In some instances, "obvious to try" reasoning can support a finding of obviousness. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." See *KSR* at 1397. In this case, there is a market pressure to control the hematopoietic differentiation of stem cells (see, e.g, the abstract of Herzog), and both the number of cell cycle phases and the number of relevant growth factors are finite. If applicant intends to imply that at the time of the invention, the skilled artisan would not have been able to identify all of the growth factors and cytokines that might affect hematopoietic differentiation, the examiner might question the enablement of the invention under 35 U.S.C. § 112, first paragraph.

Applicant makes various points regarding the limitations of claims 29, 30, 61, and 62, but these limitations have been addressed in the indefiniteness rejections. See reply, page 22.

Applicant points to data in the Quesenberry declaration regarding Lin^- $rhodamine^{lo}$ $Hoechst^{lo}$ cells, but these data are not relevant to any claim other than claim 64 (the only claim that includes these limitations). See page 22 of the reply.

Regarding claim 64, the showing in the Quesenberry declaration is not persuasive of error in the rejection. The Quesenberry declaration nebulously points to "Example 1 and Figures 1-6" without clearly explaining which elements of the data are truly unexpected. Applicant has the burden to explain proffered data; see M.P.E.P. § 716.02(b). There are no comparisons to any prior art methods, much less to the methods of the cited prior art. It is not clear what aspect of the experimental results is unexpected. In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski*, 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman*, 339 F.2d 228, 144 USPQ 30 (CCPA 1964). The evidence relied upon should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter "as a class." *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler*, 429 F.2d 464, 166 USPQ 558 (CCPA 1970). See, also, *In re Lindner*, 457 F.2d 506, 173 USPQ 356 (CCPA 1972). It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi*, 759 F. 2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Klosak*, 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco*, 429 F.2d 1244, 169 USPQ 303 (CCPA 1971). *Ex parte Gelles*, 22 USPQ2d 1318 (BPAI 1992). There is no clear showing of any unexpected results here, given that at the time of the invention, the art (as evidenced by the cited references) had thoroughly investigated the effects of growth factors/cytokines and the cell cycle on multipotency and differentiation of hematopoietic stem cells.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651